

Clinical features associated with costs in early AD

Baseline data from the Predictors Study

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Abstract—Background: Few studies on cost of caring for patients with Alzheimer disease (AD) have simultaneously considered multiple dimensions of disease costs and detailed clinical characteristics. **Objective:** To estimate empirically the incremental effects of patients' clinical characteristics on disease costs. **Methods:** Data are derived from the baseline visit of 180 patients in the Predictors Study, a large, multicenter cohort of patients with probable AD followed from early stages of the disease. All patients initially lived at home, in retirement homes, or in assisted living facilities. Costs of direct medical care included hospitalizations, outpatient treatment and procedures, assistive devices, and medications. Costs of direct nonmedical care included home health aides, respite care, and adult day care. Indirect costs were measured by caregiving time. Patients' clinical characteristics included cognitive status, functional capacity, psychotic symptoms, behavioral problems, depressive symptoms, extrapyramidal signs, comorbidities, and duration of illness. **Results:** A 1-point increase in the Blessed Dementia Rating Scale score was associated with a \$1,411 increase in direct medical costs and a \$2,718 increase in unpaid caregiving costs. Direct medical costs also were \$3,777 higher among subjects with depressive symptoms than among those who were not depressed. **Conclusions:** Medical care costs and unpaid caregiving costs relate differently to patients' clinical characteristics. Poorer functional status is associated with higher medical care costs and unpaid caregiving costs. Interventions may be particularly useful if targeted in the areas of basic and instrumental activities of daily living.

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The high costs of caring for patients with Alzheimer disease (AD) are well documented.^{1–13} Costs include direct, indirect, and intangible costs.^{14,15} Direct costs include payments for medical care and other goods and services used because of the illness. These include multiple dimensions of medical care costs (e.g., nursing home care, medications, physician visits, hospitalizations) and nonmedical care costs (e.g., home health aides, respite care, adult day care). Indirect costs are imputed values of resources lost due to the illness, including premature deaths, patient and caregiver lost productivity, and unpaid caregiving time. Intangible costs are those related to pain and suffering endured by the patients and families and those related to deterioration of patient and caregiver quality of life (QoL). Variations in costs of caring for patients with AD have been explained by a number of factors. Earlier studies used gross dementia severity classification systems and estimated the

effect of disease severity on disease costs.^{6,7,9,14,16–19} More recently, several studies have examined the effects on disease costs of patients' comorbid medical conditions,^{7,9} behavioral problems,^{4,19,20} and extrapyramidal signs.¹³

Early work from the Predictors Study, a large, multicenter cohort of patients with probable AD followed from early stages of the disease, has developed and validated algorithms to predict the length of time until an individual patient required care equivalent to nursing home care or died.²¹ The predictors included sex, duration of illness, age at onset, modified Mini-Mental State Examination (mMMS) score, and the presence or absence of extrapyramidal signs or psychotic features. These clinical features were chosen because they occur early in the disease and can be assessed easily and reliably by a clinician in a standard patient visit. Further work updating these algorithms identified measures of functional capacity

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and a modified Charlson index of comorbidity as potential predictor variables.²²⁻²⁴ In the current study, we aim to extend our previous work and estimate empirically effects of these patients' clinical characteristics on disease costs.

Methods. *Sample.* The sample is drawn from the Predictors 2 cohort and consisted of 204 patients with probable AD recruited in 1998 through 2004 from three sites: Columbia University Medical Center, Johns Hopkins School of Medicine, and Massachusetts General Hospital.^{23,25,26} The study was approved by the appropriate local institutional review boards.

The inclusion and exclusion criteria are fully described elsewhere.^{23,25,26} In brief, subjects met Diagnostic and Statistical Manual of Mental Disorders (3rd rev. ed.) criteria for primary degenerative dementia of the Alzheimer type and National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD. Enrollment required an mMMS score of ≥ 30 , equivalent to a score of approximately ≥ 16 on the Folstein Mini-Mental State Examination (MMSE).^{27,28} Because the patients are followed at academic AD centers, they are well characterized with high degrees of certainty in their AD diagnosis. Overall, from both Predictors cohorts, 109 patients have had autopsy examinations. Postmortem diagnostic procedures have been completed for 96 patients, 96% of whom had AD-type pathologic changes.

For the current study, we excluded 15 patients (7.3%) living in nursing homes at baseline because patterns of care utilization and cost differ substantially for nursing home patients.²⁹ We further excluded nine patients (4.4%) with missing cost data from our analysis sample. The final analysis sample consisted of 180 patients.

Measures. The current study is based on data collected at the initial visit, during which various sociodemographic and clinical characteristics were assessed. Recruitment of patients in the Predictors Study began in 1998. For the analysis sample in this study, initial baseline data were collected for 13.3% of patients in 1998, 8.3% in 1999, 24.3% in 2000, 26.0% in 2001, 15.5% in 2002, 11.1% in 2003, and 1.1% in 2004. Detailed information was collected on patients' healthcare utilization during the previous year.

Measures of healthcare utilization and cost. Patients and informants reported utilization of seven domains of medical and nonmedical care. Medical care included hospitalization, outpatient treatment and procedures, assistive devices, and medications. Nonmedical care included home health aides, respite care, and adult day care. Patients and informants also reported on unpaid caregiving time patients received. We annualized utilization rates when domains of utilization were reported for three months (outpatient medical test, treatments, and procedures; nonmedical care; unpaid caregiving) and 6 months (medications).

Medical care. Hospitalizations. Patients and informants reported number of hospital stays during the previous year and reasons for each admission. We solicited consent to obtain patients' hospital records as necessary. We used the 1999 data set of HCUPnet, Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality (AHRQ), to categorize hospitalizations into the following 14 major diagnostic categories (MDCs): infectious and parasitic diseases; injuries, poisons, and toxic effects of drugs; neoplasm; endocrine, nutritional, and metabolic diseases; mental diseases and disorders; diseases of the respiratory system; diseases of the circulatory system; diseases of the musculoskeletal system and connective tissue; diseases of the digestive system; diseases of the genitourinary system; diseases of the skin, subcutaneous tissue, and breast; diseases of blood, blood-forming organs, immunologic disorders; diseases of the nervous system; and all other disease categories.³⁰ When more than one diagnosis was reported, the hospitalization was attributed to the diagnosis with the highest per-diem cost. No additional cost was attributed. We found payment rates in the northeast to be in the median of the price range, so we used the overall national average rate per overnight hospital stay for each MDC to compute the cost of hospitalizations.

Outpatient medical tests, treatments, and procedures. Patients and informants reported the type and number of outpatient medical tests, treatments, and procedures patients received in the previous 3 months. We used Current Procedure Terminology codes

from the American Medical Association to identify each item. We used 1999 national average participating payment rates from Clinical Diagnostic Laboratory Fee Schedule established by the Centers for Medicare and Medicaid Services (CMS) to compute the costs.³¹ When the payment rate for a particular item was not listed, we obtained price data from various Web sites and used the average price from different sources as the price for the item.

Assistive devices. Patients and informants reported the type and number of assistive devices (e.g., walkers, grab bars) that were purchased during the previous year. We used Healthcare Common Procedure Coding System, established by CMS, to identify each item reported. We used 1999 payment rates for noninstitutional providers to compute the costs of medical equipments.³² We examined overall ceiling and floor values, compared them with the values for the three states in which the Predictors sites were located, and chose to use the ceiling values as these correspond most closely to values for the site's states. When the payment rate for a particular item was not listed, we obtained price data from various Web sites and used the average price from different sources as the price for the item.

Medications. Patients and informants reported detailed information on the medications the patient took during the last 6 months, including the name of the drug, number of days taking the drug, and number of pills per day. Prices for prescription medications were taken from the 2000 Red Book.³³ For over-the-counter medications not listed in the Red Book, average price across all brands were taken from www.cvs.com.

Nonmedical care. Patients and informants also reported utilization of overnight respite care, adult daycare, and home health aides in the previous 3 months. For adult daycare and home health aides, patients and informants reported number of days, average hours per day, and hourly cost for using the service. Because prices of overnight respite care were not asked in the questionnaire, we used national average cost of nursing home care (\$130 per day) as its estimated unit price.⁴

Unpaid caregiving cost. Unpaid caregiving time was asked for up to three caregivers (primary caregiver and two other caregivers) on basic and instrumental activities of daily living (ADLs). Basic ADLs (BADLs) included eating, dressing, and personal care (e.g., bathing, toileting). Instrumental ADLs (IADLs) included shopping, chores, personal business, and transportation. Hours of unpaid care provided per day for each caregiving task were asked in the following categories: 0, up to 3 hours, 3 to 6 hours, 6 to 9 hours, 9 to 12 hours, and more than 12 hours. We transformed the categories into continuous values using the mean of each category as the estimated hours of care provided. For subjects who reported more than 12 hours per day for a particular type of task, we top-coded the values to 12 hours. We followed the literature and top-coded total hours of care provision for IADL and BADL tasks at 16 hours to provide 8 hours of sleep for the caregivers.³⁴ No caregiver provided more than 16 hours of care per day at baseline. We used the national average hourly earning for all private industries (\$14.32) as the hourly wage rate to estimate unpaid caregiving costs.³⁵

Clinical and sociodemographic characteristics. A number of clinical features that occur early in the disease and can be assessed easily and reliably by a clinician have been shown to be associated with costs, mortality, or institutionalization among dementia patients. We examined the association between the following factors with health services utilization and costs.

Cognitive status. We used the MMSE to examine patients' cognitive function.²⁷ Higher scores indicate better cognitive status. We categorized MMSE into two groups at a score of 20 because it marked a transition from mild (MMSE > 20) to moderate (MMSE \leq 20) dementia.

Functional capacity. We used the Blessed Dementia Rating Scale (BDRS) Parts I (IADLs) and II (BADLs) to assess patients' functional capacity.³⁶ This is a 17-point scale with higher scores indicating worse functional status. As there are no established cutoff points for this scale, we categorized the BDRS scores into low- and high-functioning groups at the median score for ease of presenting descriptive results.

Psychotic symptoms. Patients' psychotic symptoms were rated using the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD), a semistructured interview administered by a physician or a trained research technician. Most CUSPAD items indicate presence or absence of a particular symp-

tom. Reliability and validity of each symptom category of CUSPAD have been established in dementia populations with κ coefficients of 0.61 to 0.63.³⁷ For delusions, the following categories are included: general delusions (strange ideas, unusual beliefs), paranoid (people are stealing things, unfaithful wife/husband, unfounded suspicions), abandonment (accusing caregiver of plotting to leave him/her), somatic (the patient has cancer or other physical illness), misidentification (people are in the house when nobody is there, someone else is in the mirror, spouse/caregiver is an imposter, the patient's house is not his/her home, the characters on television are real), and a miscellaneous category. Four categories of hallucinations were recorded: auditory, visual, tactile, and olfactory. Patients were considered to have hallucinations if they had hallucinations in any of the above four sensory modalities. For illusions, the informant answered the question "Has the patient reported that one thing is something else (e.g., saying that a pillow looks like a person or a light bulb looks like a fire starting)?" We constructed a dichotomous variable to indicate the presence of any delusions, hallucinations, or illusions as evidence for psychotic symptoms.

Behavioral problems. Patients' behavior problems also were measured using CUSPAD ($\kappa = 0.67$).³⁷ As in previous work,³⁸ the following five items were used to assess patients' behavioral disturbances: wandering away from home or caregiver, verbal outbursts, physical threats or violence, agitation or restlessness, and sundowning (more confusion at night or during evening compared with the day). We constructed a dichotomous variable to indicate the presence of any of these five symptoms as evidence of behavioral problems.

Depressive symptoms. Items for depressive symptoms also were measured using CUSPAD ($\kappa = 0.73$).³⁷ These items included depressed mood (sad, depressed, blue, down in the dumps), difficulty sleeping, and change in appetite. As in previous work,³⁹ we constructed a dichotomous variable indicating patients having depressive symptoms to be those reporting depressed mood and having either difficulty sleeping or change in appetite.

Extrapyramidal signs. Extrapyramidal signs (EPSs) were assessed by trained examiners using a modified Unified Parkinson's Disease Rating Scale (UPDRS) that has good interrater reliability properties in dementia populations.^{40,41} The following 11 items were rated on a Likert scale of 0 to 4 (with 0 being normal and 4 indicating maximum impairment): speech, facial expression, tremor at rest, neck rigidity, right arm rigidity, left arm rigidity, right leg rigidity, left leg rigidity, posture, gait, and bradykinesia. In accordance with our previous work,²³ we constructed a dichotomous indicator for the presence of EPS if any item was rated 2 or higher. The reasons for this cutoff are as follows: 1) We previously demonstrated good interrater reliability for at least mild to moderate severity (score of 2 or more indicating mild severity),⁴⁰ and 2) this level of severity is also more likely to be noted by the average clinician.

Comorbid conditions. We used patients' medical histories to construct a modified version of the Charlson index of comorbidity.²²⁻²⁴ Comorbid conditions included items for myocardial infarct, congestive heart failure, peripheral vascular disease, hypertension, chronic obstructive pulmonary disease, arthritis, gastrointestinal diseases, mild liver disease, diabetes, chronic renal disease, and systemic malignancy. No patients reported clinical strokes, metastatic tumors, or AIDS at baseline.

Duration of illness. A neurologist estimated the disease duration based on interviews with the patient and informant.

Sociodemographic characteristics. We included in our analysis a number of sociodemographic characteristics of the patients including age, gender, education, and marital status.

Analysis. We compared the characteristics of patients who were excluded from the analysis with those included in the study and compared patients' sociodemographic characteristics across sites. Because utilization rates of nonmedical care (home health aides, respite care, and adult day care) are relatively low, we combined them into one category in the analyses. We compared utilization rates and costs for each domain of medical care, nonmedical care, and unpaid care by the following patient clinical characteristics: psychotic symptoms, EPSs, depressive symptoms, behavioral problems, functional status, cognition, and comorbid conditions. For bivariate analyses, we categorized these clinical variables into presence or absence of symptoms or high and low groups. Group comparisons of categorical variables (e.g., utiliza-

tion) were performed using χ^2 tests, and comparisons of continuous variables (e.g., costs) were performed using nonparametric Wilcoxon rank sum test. We chose the Wilcoxon rank sum test over the Student t test because the cost variables are highly skewed. All cost values are adjusted to constant 2004 dollars using the medical care component of the Consumer Price Index.³⁵

We hypothesized that direct and indirect costs were differentially associated with different clinical characteristics. We estimated separate equations for total medical costs and indirect costs in the previous year using multivariate methods. Because cost data are highly skewed, results from usual estimation methods (e.g., ordinary least squares [OLS]) will be biased. We examined the appropriateness of distributional family and link functions using the modified Park test⁴² and chose generalized linear models (GLM) with γ family and log link as our estimation method. A competing model for cost estimation is the OLS regression on log-transformed dependent variable with retransformation of the estimates to the natural scale using the Duan smearing estimator.⁴³ However, evidence in the recent literature suggests a number of problems related to retransformation.^{42,44} In particular, retransformation may lead to biased results if data are heteroscedastic in a continuous variable or multiple covariates, which often occurs in cost data. We chose the GLM model over the log OLS model because accumulating evidence in the literature suggests that the performance of GLM models may be superior in terms of providing robust, unbiased estimation results.^{45,46} We tested the goodness of fit of our estimation models using modified Hosmer-Lemeshow test.⁴⁷ If the link function is correct and the specification of the covariates are appropriate, then Hosmer-Lemeshow test statistic should not be significantly different from zero. Because only 17% of the subjects ($n = 31$) used nonmedical care, we did not estimate a cost equation for nonmedical care. We included all of the identified clinical characteristics in the estimation model to examine the marginal effect of each variable on the dependent variables. MMSE and BDRS scores were entered as continuous scale scores. Psychotic symptoms, behavioral problems, and depressive symptoms, all of which were measured in the CUSPAD, were entered as dichotomous variables because previous research report that it is difficult to rank CUSPAD scores and it is best to construct dichotomous variables from it.^{24,38} All analyses were performed using Stata 8.0.⁴⁸

Results. Sociodemographic and clinical characteristics.

Compared with others, patients living in nursing homes were older, more likely to be women, and less likely to be married (results not shown). They also had lower MMSE scores and more comorbid conditions. The nine patients who had missing cost information were not significantly different in sociodemographic characteristics and disease severity from patients with complete cost information.

Sociodemographic and clinical characteristics of the subjects at baseline are presented in table 1. The average patient was 75.4 years old. Slightly over half were men (56.1%). The patients in the sample were largely non-Hispanic white (93.3%), well educated (with an average of 14.5 years of schooling), and either married (65.6%) or widowed (26.7%). There were no differences in subjects' sociodemographic characteristics across sites.

Because of the study inclusion criteria, patients were at early stages of AD. Most patients (95%) were mildly demented with a Clinical Dementia Rating Scale (CDR) score of 1, and 5% were moderately demented with a CDR score of 2.⁴⁹ Neurologists' estimate of average duration of illness was 4.2 years (SD = 2.2); 90% of the patients had symptoms for 6 or fewer years. Mean MMSE score at baseline was 22.1 (SD = 3.8), and mean BDRS score was 3.5 (SD = 2.3). Whereas almost all patients had some IADL limitations, two-thirds (64%) were not limited in BADLs. Behavioral problems (42.2%) and psychotic symptoms (32%) were common by CUSPAD ratings. About 20% had depressive symptoms, and 13.3% exhibited EPSs. On average, pa-

Table 1 Baseline sociodemographic and clinical characteristics of patients (n = 180)

| | |
|---|----------------------|
| Age, mean (SD); y | 75.4 (7.6) |
| Younger than age 65, n (%) | 16 (8.9) |
| Age 65–74, n (%) | 54 (30.0) |
| Age 75–84, n (%) | 89 (49.4) |
| Age 85 or older, n (%) | 21 (11.7) |
| Men/women, n (%) | 101 (56.1)/79 (43.9) |
| Race | |
| White, n (%) | 168 (93.3) |
| Black, n (%) | 10 (5.6) |
| Other, n (%) | 2 (1.1) |
| Years of schooling completed, mean (SD) | 14.5 (3.2) |
| Marital status | |
| Married, n (%) | 116 (66.1) |
| Widowed, n (%) | 47 (26.1) |
| Other, n (%) | 14 (7.7) |
| MMSE, mean (SD) | 22.1 (3.8) |
| BDRS, mean (SD) | 3.5 (2.3) |
| EPS, n (%) | 24 (13.3) |
| Psychotic symptoms, n (%) | 59 (32.8) |
| Behavioral problems, n (%) | 78 (43.3) |
| Depressive symptoms, n (%) | 36 (20.0) |
| Years since symptoms, mean (SD) | 4.2 (2.2) |
| Comorbid conditions | |
| None, n (%) | 90 (50.0) |
| One, n (%) | 60 (33.3) |
| Two or more, n (%) | 30 (16.7) |
| Site | |
| Columbia, n (%) | 88 (48.9) |
| Johns Hopkins, n (%) | 48 (26.7) |
| Massachusetts General, n (%) | 44 (24.4) |

MMSE = Mini-Mental State Examination (range = 0–30); BDRS = Blessed Dementia Rating Scale (range = 0–17); EPS = extrapyramidal signs.

tients had fewer than one comorbid condition (mean = 0.7, SD = 0.8); half of the patients did not have any comorbid conditions.

Utilization and annual per-capita costs. Table 2 presents data on utilization rates for each component of medical care, nonmedical care, and unpaid care by patients' clinical characteristics. Because of high rates of medication use (96.1%), all patients used some type of medical care during the previous year. On average, 21.7% reported being hospitalized; 73.3% reported receiving outpatient medical tests, treatments, or procedures; and 41.7% reported using assistive devices; 17.2% used some type of nonmedical care, mostly home health aides (11.1%) or adult day care (7.2%). Almost all patients (92.8%) received unpaid care.

In general, utilization rates were higher among patients with more severe clinical features. Because of almost universal use, utilization of medications and unpaid care were not significantly different by any of the clinical characteristics. Patients who were more functionally dependent used significantly more services in all other types of services. Those with worse cognition were more likely to use assistive devices and nonmedical care. Compared with those without any symptoms, patients exhibiting psychotic symptoms were significantly more likely to use outpatient treatment and tests, assistive devices, and nonmedical

care. Patients with EPS and those with behavioral problems were significantly more likely to use assistive devices and nonmedical care than those without EPS or behavioral problems.

Translating utilization into the costs, we estimated that average annual cost per patient was \$7,918 for medical care and \$1,842 for nonmedical care. The largest components of medical care costs were hospitalizations (\$3,264, 41% of total costs) and medications (\$2,855, 36% of total costs). Costs of outpatient treatments, tests, and procedures (\$1,655) also were substantial, accounting for approximately 21% of total medical care costs. Patients received an average of 23 hours of unpaid care per week. We estimated annual unpaid costs to be \$15,906, almost twice the cost of all medical care and nonmedical care costs combined.

Similar to utilization rates, costs were almost universally higher among patients with worse clinical features. Unadjusted differences in total medical costs between patients with worse and better clinical features were \$2,657 for psychotic symptoms, \$4,767 for depressive symptoms, \$3,352 for functional dependence, and \$3,209 for comorbid conditions. Unadjusted differences in unpaid caregiving costs between patients with worse and better clinical features were \$2,589 for psychotic symptoms, \$3,824 for behavioral problems, and \$9,579 for functional dependence.

Adjusted medical and unpaid caregiving costs. Table 3 presents regression results of total medical costs and unpaid costs on patients' clinical and sociodemographic characteristics. Because costs were highly skewed (2.64 for total direct medical care, 4.67 for total direct nonmedical care, and 1.85 for unpaid caregiving cost), we chose GLM as our estimation method. The Hosmer–Lemeshow test found no evidence of systematic misfitting in either estimation equation. Subjects' functional status and depressive symptoms were significantly associated with medical care costs. Controlling for other variables, a 1-point increase in the BDRS score increased medical cost by \$1,411. Medical costs were \$3,777 higher among subjects with depressive symptoms than those who were not depressed. Although only marginally significant, presence of psychotic symptoms, number of comorbidities, duration of disease, and older age also were associated with total medical costs. There were no gender or site differences in total medical costs. On the other hand, the only variable that was significantly associated with unpaid caregiving costs was subjects' functional status. A 1-point increase in the BDRS scores increased unpaid caregiving costs by \$2,718.

Discussion. In this study, we estimated empirically the marginal effects of various clinical characteristics on disease costs during early stages of AD. At baseline, the patients in the sample were mildly impaired in cognition (mMMS score \geq 30), few patients had more than one psychotic or depressive symptom, and EPS prevalence was low. Results show that medical care costs and unpaid caregiving costs respond differently with patients' clinical characteristics. Patients' functional status, depressive symptoms, psychotic symptoms, comorbidities, duration of symptoms, and age were strongly associated with medical care costs. Contrary to medical care costs and consistent with the literature,^{19,50} we found

Table 2 Percent of patients using each type of services, by clinical characteristics (*n* = 180)

| | Direct medical care | | | | | |
|----------------------------|---------------------|-----------------|----------------------|-------------------|------------------------|---------------|
| | Medication | Hospitalization | Outpatient treatment | Assistive devices | Direct nonmedical care | Indirect care |
| All sample | 96.1 | 21.7 | 73.3 | 41.7 | 17.2 | 92.8 |
| Psychotic symptoms | | | | | | |
| Not present | 95.1 | 18.7 | 67.5‡ | 35.8† | 10.6‡ | 91.9 |
| Present | 98.2 | 28.1 | 86.0 | 54.4 | 31.6 | 94.7 |
| Extrapyramidal signs | | | | | | |
| Not present | 96.2 | 20.5 | 71.8 | 38.5† | 15.4* | 92.9 |
| Present | 95.8 | 29.2 | 83.3 | 62.5 | 29.2 | 91.7 |
| Depressive symptoms | | | | | | |
| Not present | 95.8 | 19.4 | 71.5 | 39.6 | 16.7 | 93.8 |
| Present | 97.2 | 30.6 | 80.6 | 50.0 | 19.4 | 88.9 |
| Behavioral problems | | | | | | |
| Not present | 94.2 | 19.2 | 70.2 | 32.7‡ | 12.5† | 94.2 |
| Present | 98.7 | 25.0 | 77.6 | 53.9 | 23.7 | 90.8 |
| BDRS | | | | | | |
| Higher function | 95.1 | 15.7‡ | 65.7‡ | 27.5‡ | 6.9‡ | 92.2 |
| Lower function | 97.4 | 29.5 | 83.3 | 60.3 | 30.8 | 93.6 |
| MMSE | | | | | | |
| ≤20 (moderate) | 97.5 | 20.8 | 69.2* | 38.3 | 11.5* | 82.5 |
| >20 (mild) | 93.3 | 23.3 | 85.0 | 48.3 | 21.7 | 93.3 |
| Years since symptoms began | | | | | | |
| ≤4 | 97.2 | 22.2 | 77.8 | 45.4 | 16.7 | 93.5 |
| >4 | 94.4 | 20.8 | 66.7 | 36.1 | 18.1 | 91.7 |
| No. of comorbidities | | | | | | |
| 0 | 97.8 | 17.8† | 70.0 | 46.7 | 12.2 | 86.7 |
| 1 | 93.4 | 19.7 | 80.3 | 32.8 | 21.3 | 100.0 |
| 2 or more | 96.6 | 37.9 | 69.0 | 44.8 | 24.1 | 96.6 |

* $p < 0.10$, † $p < 0.05$, ‡ $p < 0.01$ from χ^2 tests.

BDRS = Blessed Dementia Rating Scale (range = 0–17); MMSE = Mini-Mental State Examination (range = 0–30).

that variations in unpaid caregiving cost were only significantly associated with patients' functional status. Partially owing to the fact that patients were at early stages of AD at baseline, we were unable to estimate the effects of the severity of clinical features on costs. Several other variables also may be importantly associated with indirect costs. For examples, behavioral problems and number of comorbid conditions were associated with higher indirect costs; and the presence of EPS was surprisingly associated with lower indirect costs. However, possibly because of the small sample size, the standard errors of these estimates were so large that the coefficients were not statistically significant.

It should be noted that the effects of cognitive decline may be underestimated in our models because cognition, functional status, and depression may be correlated, and cognitive impairment may lead to functional decline and depression. We examined the correlation between these factors. Patients' MMSE and BDRS scores were highly correlated ($r = -0.3427$, $p < 0.001$), but patients' MMSE scores were not significantly different between those with depressive symptoms (mean MMSE = 40.4, SD = 7.0) and those without (mean MMSE = 42.3, SD = 6.8). To address the issue of potential underestima-

tion of the effects of cognition, we re-estimated our models by entering patients' MMSE scores alone. Results show that MMSE scores were not significant in either equation. Perhaps because the patients in our sample were in the early stages of AD, MMSE scores were not significantly associated with costs. However, the conclusion that functional status is more important than cognition should not be drawn from these analyses. In future studies, we will examine the effect of cognitive decline on function and costs using longitudinal data.

We based the cost estimates on payment rates from a number of sources (CMS, AHRQ, the Red Book). No cost-to-charge ratios were therefore applied. We did not find a national average cost for overnight respite care in the literature and used the cost of nursing home care (\$130 per day) as its estimate.⁴ We also considered using the cost for assisted living care (\$108 per day) as an alternative estimate for the cost of respite care.⁴ Because so few patients used respite care, our estimates of nonmedical care costs would not be substantially changed. Large proportion of service utilization occurred during 1999 through 2001. We used 2000 price data and adjusted cost values to constant 2004 dollars so our cost estimates would more closely reflect the time of utiliza-

Table 3 Generalized linear models of baseline medical care and indirect care costs (*n* = 180)

| Variables | Direct medical care, coefficient (SE) | Indirect care, coefficient (SE) |
|---|---------------------------------------|---------------------------------|
| Psychotic symptoms (1 = present, 0 = absent) | 2,477* (1,436) | -733 (3,467) |
| Extrapyramidal signs (1 = present, 0 = absent) | -321 (2,057) | -3,761 (4,619) |
| Depressive symptoms (1 = present, 0 = absent) | 3,777† (1,687) | -157 (3,777) |
| Behavior problems (1 = present, 0 = absent) | 112 (651) | 1,389 (1,539) |
| BDRS score | 1,411‡ (542) | 2,718‡ (1,354) |
| No. of comorbidities | 1,741* (950) | 2,800 (2,116) |
| MMSE score | 56 (211) | -354 (443) |
| Years since symptoms began ≤4 (1 = yes, 0 = no) | 2,305* (1,297) | 1,966 (3,178) |
| Age 65 or older (1 = yes, 0 = no) | 4,076* (2,210) | 508 (5,101) |
| Women (1 = yes, 0 = no) | -1,990 (1,320) | -14 (3,130) |
| Site (reference = Columbia) | | |
| Johns Hopkins | -1,564 (1,666) | -2,860 (3,754) |
| Massachusetts General | -1,024 (1,595) | -7,621 (3,678) |
| Constant | 20,856‡ (5,407) | 23,946† (11,571) |
| Log likelihood | -1,767.256 | -1,897.378 |
| Akaike Information Criterion | 19.891 | 21.345 |
| Bayesian Information Criterion | -721.942 | -771.826 |
| Pregibon link test (χ^2_1), <i>p</i> value | 0.163 | 0.505 |
| Hosmer-Lemeshow test ($F_{10,170}$), <i>p</i> value | 0.523 | 0.540 |

* $p < 0.10$, † $p < 0.05$, ‡ $p < 0.01$.

BDRS = Blessed Dementia Rating Scale (range = 0–17); MMSE = Mini-Mental State Examination (range = 0–30).

tion. We recognize that the validity of these estimates depends on the generalizability of the data and the accuracy of the unit prices, and actual resource costs may differ from our estimates. However, estimating the actual cost of care for each medical center would be costly and subject to measurement error as well. Furthermore, the actual cost would be specific to the site, whereas the payment schedules we used are reasonable estimates of what would be paid in general. The annualization procedure we used should not bias the multivariate findings, because it simply introduces a constant to the dependent variables.

Although providing comprehensive estimates of direct and indirect costs of caring for patients in early stages of AD is not a primary goal of this study, our results indicate the validity of the data collection process used in the Predictors Study. Using our gross costing method, we estimate that annual cost per patient amounted to \$17,232 for unpaid care and \$7,929 for direct medical care. The largest components of medical care costs were hospitalizations (\$3,310, 41.7%) and medications (\$2,853, 36.0%). For this group of mildly demented patients, nonmedical care costs (\$1,604 per year) were comparatively smaller in magnitude. The magnitude of these results is consistent with existing studies and again shows that unpaid caregiving costs are more than twice that of total direct costs among AD patients living in the communities.^{17,51}

Our multivariate results help provide information for deriving estimates of potential cost savings if interventions that aim to improve patients' functioning are developed. Results suggest that small differences in functioning may be associated with large differ-

ences in medical care costs and unpaid caregiving costs. An intervention that improves BDRS score among AD patients could be expected to yield average savings of \$1,411 per year in medical costs and \$2,718 in unpaid caregiving costs. As a secondary analysis, we tested our models using BDRS factors instead of the total score to examine which specific domains were most sensitive to costs. As a group, the BDRS factors were significantly associated with both higher medical costs and higher unpaid caregiving costs. In particular, the IADL factor was associated with indirect cost and the BADL factor was associated with higher medical costs. Interventions may be particularly useful if improvements are in the areas of IADLs and BADLs.

It is notable that the potential cost savings we estimated are generated from a sample of mildly demented patients. An earlier study found that although most cost savings may not be realized immediately, a delay in disease progression for patients at early stages of the disease would yield greater cost savings than the same delay experienced by patients at later disease stages.⁵² Because subjects have been followed closely in our study, our future work will address issues of lifetime cost savings more appropriately by using longitudinal analyses.

Our study has several limitations. First, results reported here are from a cross-sectional analysis. An important limitation of the cross-sectional design is that the relationships reported can only be interpreted as associations. Although certain clinical features can lead to higher costs, it also is possible that low spending on healthcare indicates insufficient medical care and results in poor health. Future work

using longitudinal data is necessary to determine if the relationships reported in this study are consistent over time.

Second, although our estimate of indirect costs already are substantial, it is important to note that we only included the cost of caregivers' time. Indirect costs also may include those related to caregivers' lost productivity, and reduced hours of work and income. However, reductions in work hours due to caregiving and hours spent on caregiving may overlap and lead to possible double counting of caregiving costs. In this sample, fewer than 15% of the caregivers who worked reported reducing work hours because of caregiving responsibilities. Among these caregivers, average work hour reduction was 2.3 hours per week. In this sample and at the early stages of the disease, costs from reduced work hours are therefore relatively minor. It also is important to consider other intangible costs such as patient and caregiver QoL. Although the QoL questions were included in the study, valuation of such costs is difficult and beyond the scope of this study. In this study, we used national average hourly earning for all private industries as the hourly wage rate to estimate the cost of caregivers' time. As market wages may not accurately reflect caregivers' opportunity cost of time, another method is to estimate the caregivers' wage rate in computing time cost. Possible differences in results in using these methods have implications for comparing direct and indirect costs of care. An earlier study on unpaid dementia caregiving costs suggests that results from using these two methods are similar.⁹

Data on patients' healthcare utilization from this study were reported by patients and informants. Most of the informants were the patients' primary caregivers. Studies have shown that caregivers are able to accurately report medical information of their care recipients.^{53,54} There is no reason to believe our sample will be systematically different. Patients were selected from tertiary care university hospitals and specialized diagnostic and treatment centers and thus represent a nonrandom sample of those affected by AD in the population. The patients in our sample also were predominantly white and highly educated. Caution is needed in generalizing the results of this study to patients with lower levels of education and income and to community AD patients. Future research will need to examine the relationship between costs and the potential variables in samples that are more representative of the general population. However, because patients were drawn from multiple locations, the generalizability of our findings is enhanced.

Finally, our study is limited by the relatively small sample size. This points to the common tradeoff between national representativeness and refinement of diagnosis and richness of clinical variables in smaller studies. Studies from large national surveys typically do not have detailed information on patients' clinical characteristics. Studies that rely on

administrative databases (e.g., claims data) typically find only patients that are at more severe stages of the disease. Our data, though smaller in sample size, capture patients at early stages of the disease and have a substantially richer set of accurately assessed clinical characteristics. A major contribution of the current analyses lies in the careful diagnosis and clinical follow-up that patients received. Clinical diagnoses took place in university hospitals with specific expertise in dementia and were based on uniform application of widely accepted criteria via consensus diagnostic conference procedures. The accuracy of the AD diagnoses has been confirmed in a high proportion (96%) of those who have come to postmortem evaluation.²³ Finally, confidence in clinical characteristics is further increased because they were ascertained and coded in a standardized fashion using validated scales rather than clinical assessments. With the detailed data on clinical characteristics, our study complements those using large national datasets.

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Clinical features associated with costs in early AD: Baseline data from the Predictors Study

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